A6 CONT.

--39. The method of claim 38, wherein the cytokine of the immunoconjugate is a lymphokine.--

REMARKS

Claims 1-27 are pending. Claims 1-27 stand rejected. Applicant amends claims 1, 10, 12, 19, 20 and 25. Applicant adds new claims 28-39. Accordingly, after entry of this Amendment, claims 1-39 will be pending for examination. Applicant submits that the amendments and new claims introduce no new matter and that claims 1-39 are in condition for allowance.

Amendments to the Claims

Independent claims 1, 12 and 20 are amended to correct antecedent basis and to delete unnecessary language.

Dependent claims 10, 19 and 25 are amended to remove "lymphokine" from the Markush group.

Applicant submits that these amendments introduce no new matter.

New Claims

Applicant adds new claims 28-39. New claims 28-30 define the cytokine of an immunoconjugate as a lymphokine. Support for new claims 28, 29, and 30 is found in the application as filed at least in original claims 10, 19, and 25, respectively.

New claims 31-39 generally recite methods of reducing the size of a tumor including administering an immunoconjugate of the invention and an angiogenesis inhibitor. Support for claims 31-39 is found in the application as filed at least at page 3, the second through fourth paragraphs; in Example 5 found on pages 33 and 34; and in original claims 1, 2 and 12-19.

Accordingly, Applicant submits no new matter is introduced by the new claims.

Claims Objections

Dependent claim 10 is objected to as using improper/incomplete Markush language. Without acquiescing to the objection, Applicant has amended claim 10 to remove a lymphokine from the Markush group. Accordingly, Applicant respectfully requests that this objection be reconsidered and withdrawn.

Non-Statutory Double Patenting Rejection

Claims 1-27 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-27 of co-pending application Serial No. 09/293,042.

Applicant respectfully requests that this provisional rejection be held in abeyance until a determination of allowable subject matter is made.

35 U.S.C. § 112, First Paragraph Rejections

Claims 1-27 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. According to the Office action, the specification generally does not enable any person skilled in the art to practice the invention commensurate in scope with the claims without undue experimentation.

Applicant submits, as discussed with Examiner Gary Kunz on December 1, 2000, that the rejections under 35 U.S.C. § 112 cannot be appropriately responded to because the Office action addresses prostaglandin inhibitors while the claims in the instant case are directed to the use of angiogenesis inhibitors. The Office action appears to cite to the page and line numbers of the specification of a co-pending patent application, i.e., U.S. Serial No. 09/293,042, which is directed to the use of immunoconjugates and prostaglandin inhibitors.

Accordingly, Applicant respectfully requests that the rejections under 35 U.S.C. § 112 be reconsidered and withdrawn, or that another non-final Office action issue to permit Applicant an opportunity to reply to any rejection properly presented for the first time.

35 U.S.C. § 103 Rejections

Claims 1-2 and 4-27 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Gillies et al. (WO 92/08495) ("Gillies") in view of O'Reilly et al. (Cell 88: 277-285 (1997)) ("O'Reilly").

According to the Office action, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the immunoconjugate taught by Gillies and the angiogenesis inhibitor taught by O'Reilly in a method of inducing a cytocidal immune response against a targeted tumor cell. More specifically, the Office action states that one skilled in the art would have been motivated to use the immunoconjugate comprising an antibody and a cytokine taught by Gillies and the angiogenesis inhibitor taught by O'Reilly in a method of inducing a cytocidal immune response against a tumor cell because tumor cells have two distinct cell

populations, a tumor cell population and an endothelial cell population, and that combined treatment of both cell populations may be better than treatment of either cell population alone.

O'Reilly suggests that combined treatment of the two cell populations of a tumor may be inhibited by agents that selectively or specifically target those cell populations, i.e., cytotoxic chemotherapy and antiangiogenic therapy.

In contrast, Applicant's claimed invention is directed to a method of inducing a cytocidal immune response against a preselected cell-type by administering an immunoconjugate which includes a cytokine that induces the immune response, and an angiogenesis inhibitor. Applicant's claimed invention uses a cytokine, not a cytotoxic agent, to induce an immune response. That is, the immunoconjugate itself is not cytotoxic, but rather, induces an immune response which in turn kills or reduces the viability of the preselected cell-type.

Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination. Gillies does not teach, suggest, or motivate using an angiogenesis inhibitor in combination with an immunoconjugate. As stated above, O'Reilly does not teach, suggest or motivate using an immunoconjugate which is capable of inducing an immune response against a preselected cell-type. Accordingly, Applicant submits that the Gillies and O'Reilly were improperly combined and respectfully requests reconsideration and withdrawal of this rejection.

Moreover, a proper rejection under 35 U.S.C. § 103 requires not only that the prior art suggest to one of ordinary skill in the art that the claimed combination be made, but also that the prior art must provide a reasonable expectation of success. As stated previously, Applicant's claimed invention is directed to a method of inducing an immune response against a preselected cell-type. To facilitate an immune response, a cytokine of an immunoconjugate bound to a preselected cell-type requires the cells related to the immune response, e.g., T cells or natural killer cells, to have or gain access to the preselected cell-type. Such access often is achieved via delivery through blood vessels. However, treatment of an immunoconjugate-targeted preselected cell-type with an agent that reduces or inhibits the formation of new blood vessels, e.g., an angiogenesis inhibitor, would be expected to reduce or eliminate the immune response against the preselected cell-type thereby rendering the immunoconjugate ineffective for its intended purpose. Consequently, a skilled artisan would not possess the necessary reasonable expectation of successfully administering an immunoconjugate to induce an immune response along with an angiogenesis inhibitor. Therefore, Applicant submits that the Gillies and O'Reilly were

improperly combined and further, even if they were combined as suggested, Gillies and O'Reilly do not provide the necessary expectation of success. Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

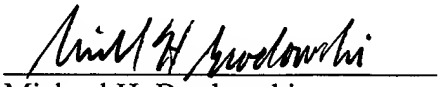
Claims 1, 11 and 26 are rejected under 35 U.S.C § 103(a) as being unpatentable over Gillies (WO 92/08495) in view of O'Reilly, (Cell 79: 315-328 (1994)) ("O'Reilly II") or Brooks et al. (Cell 79: 1157-1164 (1994)) ("Brooks") or Ingber et al. (Nature 348: 555-557 (1990)) ("Ingber").

As discussed above, Gillies in view of O'Reilly does not render Applicant's claimed invention obvious to one of ordinary skill in the art. O'Reilly II, Brooks, or Ingber do not cure the deficiencies of O'Reilly or Gillies. Furthermore, none of O'Reilly II, Brooks, or Ingber discuss combined treatment of two cell populations. Accordingly, at least for the same reasons stated above with respect to Gillies and O'Reilly, Applicant submits that Gillies and O'Reilly II, Brooks, or Ingber were improperly combined and further, even if they were combined as suggested, Gillies and O'Reilly II, Brooks, or Ingber do not provide the necessary expectation of success. Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

CONCLUSION

Based on the above amendments and remarks, Applicant respectfully submits that pending claims 1-39 are in condition for allowance and request entry as such. If the Examiner believes that a conversation with Applicant's attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 248-7012.

Respectfully submitted,



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MARKED UP VERSION OF CLAIMS SHOWING AMENDMENTS

1. (Amended) A method of inducing a cytocidal immune response against a preselected cell-type in a mammal, the method comprising:

administering to the mammal (i) an immunoconjugate comprising an antibody binding site capable of binding the preselected cell-type and a cytokine capable of inducing the cytocidal [~~a said~~] immune response against the preselected cell-type, and (ii) an angiogenesis inhibitor [~~in an amount sufficient to enhance said immune response relative to immunoconjugate alone~~].

10. (Amended) The method of claim 1, wherein the cytokine of the immunoconjugate is selected from the group consisting of a tumor necrosis factor, an interleukin, and a colony stimulating factor[~~, and a lymphokine~~].

12. (Amended) A method of inducing a cytocidal immune response against a cancer cell in a mammal, the method comprising:

administering to the mammal (i) an immunoconjugate comprising an antibody binding site capable of binding the cancer cell and a cytokine capable of inducing [~~a said~~] the cytocidal immune response against the [~~tumor~~] cancer cell, and (ii) an angiogenesis inhibitor selected from the group consisting of endostatin and angiostatin [~~in an amount sufficient to enhance said immune response relative to immunoconjugate alone~~].

19. (Amended) The method of claim 12, wherein the cytokine of the immunoconjugate is selected from the group consisting of a tumor necrosis factor, an interleukin, and a colony stimulating factor[~~, and a lymphokine~~].

20. (Amended) A composition for inducing an immune response against a preselected cell-type in a mammal, the composition comprising in combination:

(i)____an immunoconjugate comprising an antibody binding site capable of binding the preselected cell-type and a cytokine capable of inducing an immune response against the preselected cell-type in the mammal, and

(ii)____an angiogenesis inhibitor [~~in an amount sufficient to enhance said immune response induced by the immunoconjugate of the combination relative to immunoconjugate alone~~].

25. (Amended) The composition of claim 20, wherein the cytokine of the immunoconjugate is selected from the group consisting of a tumor necrosis factor, an interleukin, and a colony stimulating factor[~~, and a lymphokine~~].